REMARKS

Claims 1-31 were pending in the present application. The Examiner has withdrawn claims 4, 5, and 21-31 as drawn to nonelected inventions. While the Examiner acknowledges Applicants' election with traverse of Group I, consisting of claims 1-3 and 6-21, only claims 1-3 and 6-20 are stated to be the subject of examination. Applicants respectfully submit that claim 21 is also properly within Group I and thus should not be withdrawn from consideration. Accordingly Applicants have canceled non-elected claims 4, 5, and 22-31, without prejudice. Claim 3 has also been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claims in other applications.

The specification, at page 7, has been amended to correct an obvious grammatical error.

Claim 1 has been amended, and new claim 32 added, to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. Claim 1 has been amended to recite the language of now-canceled claim 3, "wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ." Support for this amendment is found in the specification as filed, in the section spanning page 9, line 36, to page 10, line 4. Claims 1 and 21 have been amended to recite a non-covalently bound "peptide" rather than an "antigenic molecule." Support for this amendment is found, *inter alia*, at page 7, lines 14-16, at page 9, lines 26-31, and at page 28, line 27 to page 29, line 1.

Claims 6, 8, and 14-20, have been amended to delete their dependency upon non-elected claim 4; claim 13 has been amended to delete its dependency upon non-elected claims 4 and 5, and canceled claim 3. Claims 14 and 15 have been amended to recite administering "a composition" rather than a "heat shock protein," to be consistent with the language of claim 1, upon which claims 14 and 15 depend.

Support for "a purified population of complexes," and peptides "independently selected from a population of different peptides," as recited in new claim 32, is found in Section 5.2.1 and its subsections, pp. 13-20 and the Examples in Sections 6 and 7, which describe protocols which produce a population of complexes; and at page 9, lines 27-31, page 12, lines 28-30, and at page 26, lines 26-36, which indicate that a purified population of endogenous hsp-peptide complexes comprises a population of different peptides. The present

amendments and new claim 32 are fully supported by the specification as filed, and no new matter has been added.

Summary of the Invention

Applicants respectfully submit that a brief summary of the present invention would provide a useful background for the response presented below, particularly in light of the statements provided by the Examiner in support of the imposed restriction requirement.

In the paragraph entitled ***Election/Restriction***, at page 2 of the Office Action, the Examiner states, with respect to the hsp complexes of Group I, "the immune response in the recipient *would be guided by said antigen* [that is, the hsp-bound antigenic molecule]," and, with respect to the non-complexed heat shock proteins of Group II,

> the HSP in that individual *would need to associate with a graft-specific antigen* in the recipient in order to induce the desired tolerance. Alternatively, the non-complexed HSP of Group II could also pick-up *antigens in the recipient which are not related to the grafted tissue at all and therefore have no bearing upon the recipient's response to the graft.* (Emphasis added).

The presently claimed invention is directed toward methods for the treatment and prevention of graft rejection that comprise administering compositions comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ. The purified complex can be a purified complex of many molecules of a single molecular composition (*e.g.*, as may be produced when an hsp and a single peptide are complexed *in vitro*) or a purified complex of many molecules of hsp complexed to different peptides (*e.g.* as produced when the complexes are purified as a population from within cells). It is Applicants' belief, without wishing to be held to that belief, that the basis of the claimed method is suppression of the graft-rejection process by an immunoregulatory function of heat shock proteins *per se* and is not related to any specific peptide(s) bound within that population of heat shock protein complexes. That is, the methods of the present invention can be carried out using uncomplexed heat shock proteins as well as heat shock proteins carrying a non-covalently complexed peptide. In an example of the latter instance, as Applicants have explained, "hsps complexed to the peptides with which they are

endogenously associated are used, rather than hsps not so complexed, *for purposes of convenience since the endogenous peptides copurify with the hsps.*" [1]

The specification as filed repeatedly discloses that the presently-claimed methods are distinct from methods in the literature that describe administration of graft-specific antigens. For example: (1) "Because the protection is based on the immunoregulatory role of the *hsp itself* (and not its antigenicity), the effectiveness of the treatment is general -- *unlike free peptide or other specific graft alloantigen approaches* (including where the hsp itself is an alloantigen), the treatment is not limited to a specific target alloantigen of the rejection process" [2] ; (2) "[i]n contrast to other methods reported in the literature, the use of hsps in accordance with the present invention are [sic, is] *not dependent on administration of any particular target antigen of the rejection process*" [3]; (3) "the source of hsp does not require specificity in order to effect suppression because its suppressive activity may attain specificity by acting against a previously activated T cell response, which is specific" [4]; (4) in a specific embodiment for hsp-peptide complexes used in accordance with the invention,

> the complexed peptide is not an alloantigen of the grafted tissue against which a graft rejection response may be elicited. For example, and not by way of limitation, an *autologous hsp-peptide complex* would be substantially free of any alloantigen. [5]

In contrast to methods employing administration of an identified, isolated, graft-specific antigen to induce tolerance toward that peptide antigen for treatment of *e.g.* autoimmune disease, as described in Tisch *et al.* (1994) Proc. Natl. Acad. Sci. U.S.A., 91: 437-38; *i.e.* reference "U" as cited by the Examiner on PTO form 892; hereafter, "Tisch"), the methods of the presently-claimed invention can use a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the

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1 Specification as filed, at page 9, lines 27-31, emphasis added.

2 Specification as filed, page 3, line 31, to page 4, line 1, emphasis added.

3 Specification as filed, at page 7, lines 6-9.

4 Specification as filed, at page 4, lines 7 to 11, emphasis added.

5 Specification as filed, page 9, line 36 to page 10, line 4, emphasis added.

peptide is not an alloantigen of the grafted cells, tissue, or organ, that can, *e.g.*, be isolated from any convenient organ (other than donor organ), either autologous or allogeneic, including but not limited to liver and pancreas [6] using procedures described in sections 5.2.1.1 to 5.2.1.3 of the specification as filed, from page 13, line 28 to page 20, line 4. In these instances, the purified complexes consist essentially of heat shock proteins non-covalently bound to the peptides with which they are associated in the cells from which they were isolated. Accordingly, the administered complexes, which consist essentially of a heat shock protein and a non-covalently-bound peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, can be autologous or allogeneic with respect to the patient to whom they are administered. In another embodiment of the present invention, the administered hsp-peptide complexes are formed *in vitro* between uncomplexed heat shock proteins and exogenous peptides as described in Section 5.2.5 of the specification as filed, from page 28, line 27, to page 30, line 27. Therefore, in this embodiment, either or both of the hsp or the non-covalently bound peptide can be autologous or allogeneic with respect to the patient to whom they are administered, but the claims have been amended to exclude where the peptide is an alloantigen of the grafted cells, tissue, or organ.

The Rejection Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

Claims 1-3 and 6-20 are rejected under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. At pages 3 and 4 of the Office Action, the Examiner asserts that the specification is not enabling for the claimed invention for two reasons: (1) because " the claims are drawn to the use of HSPS non-covalently complexed to 'an antigenic molecule' [and] [t]here is no specificity whatsoever in the claims regarding the nature of the antigenic molecule," and (2) because "the exemplification of the claimed invention, as depicted in Figure 1, would not lead the artisan to reasonably predict that the claimed method would be efficacious in the prevention or treatment of graft rejection." [7] Applicants traverse this rejection and respectfully request reconsideration.

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[6] Specification as filed, page 12, lines 31 to 38.

[7] Office Action, at page 3.

The present rejection appears to be based upon an alleged lack of enablement of methods directed toward induction of immune tolerance toward a graft-specific antigen by administering compositions that necessarily comprise that identified, isolated, graft-specific antigen. Applicants respectfully submit, therefore, that the present rejection is directed toward non-enablement of an invention other than the invention actually disclosed and claimed by Applicants.

In reply to this rejection, Applicants first note that "to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the *claimed invention* without 'undue experimentation'." [8] With respect to the manner in which an inventor teaches his or her invention, the United States Court of Customs and Patent Appeals has stated that:

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance ... As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* three is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. [9]

As described in the summary provided above, the claimed invention is directed toward treatment and prevention of graft rejection by administering compositions comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ. For the reasons discussed above in the section entitled Summary of the Invention, one of ordinary skill in the art reading the specification would recognize that since suppression of graft rejection according to the methods disclosed in the present specification is not dependent upon the presence of an antigenic and/or immunogenic, non-covalently bound peptide, the claimed methods reflect a property of heat shock proteins *per se*. For the same

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[8] *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (emphasis added).

[9] *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (Fed. Cir. 1971)

reasons, one of ordinary skill in the art would recognize that the invention is not limited to instances in which a heat shock protein or a peptide non-covalently bound to an hsp is a graft-specific antigen, and in fact, the claimed invention now specifies that the non-covalently bound peptide is not an alloantigen of the grafted cells, tissue, or organ.

The claimed invention also encompasses administering a composition comprising a purified complex that is not allogeneic to the patient, and can be autologous to the patient. [10] Again, one of ordinary skill would therefore recognize that the claimed invention is distinct from methods comprising administering an isolated, graft-specific antigen in order to induce tolerance. Although focused upon treatment of autoimmune disease, Tisch *et al.* is instructive (Tisch *et al.*, 1994 Proc. Natl. Acad. Sci. U.S.A., 91: 437-38, *i.e.* reference "U" cited by the Examiner on PTO form 892; hereafter "Tisch").

Two of the references cited in Tisch, *i.e.* Smilek *et. al.* (1991) Proc. Natl. Acad. Sci. U.S.A. 88: 9633-37 ("Smilek"), and Aichele *et al.* (1994) Proc. Natl. Acad. Sci. U.S.A. 91: 444-48 ("Aichele"), (Exhibits A and B, respectively), describe induction of tolerance to peptide antigens involved in autoimmune disease. Smilek discloses administration of 250 nmol of a purified eleven-residue oligopeptide designated Ac1-11[4A] emulsified in incomplete Freund's adjuvant to experimental mice at about the time of disease onset to prevent autoimmune encephalomyelitis (page 9635, Figs. 3 and 4). Similarly, Aichele discloses administration of 500 μg (~ 500 nmole [11]) or 100 μg (~ 100 nmole) of a purified nine-residue peptide designated GP33, emulsified in Freund's incomplete adjuvant to experimental mice for the prevention of LCMV-induced diabetes (page 445, Fig. 2).

In contrast to Smilek and Aichele the data provided in the present application as shown in Figure 1, and described at page 5, lines 7-28, and page 38, line 25, to page 39, line 37 of the specification as filed, reflect administration, without adjuvant, of 100 μg (~ 1 nmole [12]) of gp96 complexes isolated from two different tissue samples, to experimental

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[10] Specification as filed, at page 9, line 34 to page 10, line 11.

[11] The molar amount of peptide administered was estimated based upon an assumed molecular weight of ~ 1000 for GP33, a peptide consisting of nine amino acids. Therefore (500 x 10^{-6} gm)/(1000 gm/mole) = 500 x 10^{-9} mole = 500 nmole.

[12] Calculated using an assumed molecular weight of ~ 100,000 for gp96-peptide complexes. That is (100 x 10^{-6} gm)/(10^{5} g/mole) = 100 x 10^{-11} mole = 10^{-9} mole = 1 nmole.

mice. The results indicate that graft rejection was effectively inhibited in those mice administered 100 μg gp96 isolated from liver and from skin tissue. Moreover, one of ordinary skill in the art would also realize that any specific peptide, *i.e.* a putative graft-specific antigenic peptide, would only be found within a very small fraction of that population of gp96 complexes. [13] Therefore, representative methods described in the literature that are intended to induce tolerance by administration of a known antigenic peptide involve administration of at least 10,000-fold more peptide [14] than in the present methods if the hsp-peptide complexes were to be isolated from donor tissue. Clearly, this indicates that different immunological mechanisms are involved in these different approaches to obviating tissue rejection.

In addition, Applicants have taught that the present methods can be performed using uncomplexed heat shock proteins. In fact, as noted above, Applicants have taught that the purified complexes consisting essentially of a heat shock protein non-covalently bound to a peptide, recited in the present claims, are used primarily as a matter of convenience, since the endogenous peptides co-purify as a non-covalent complex with the heat shock proteins. That is, use of hsp-peptide complexes obviates those steps required to remove the non-covalently bound peptide to yield uncomplexed heat shock proteins.

Applicants further submit that, in view of the above discussion, the suggestion by Tisch regarding administration of "an antigen/peptide after pathogenic T cells have been activated" (Tisch, page 437, right hand column (emphasis added)) is not germane to an analysis of the present invention since the claimed methods comprise administering a

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[13] Nieland *et al.* Proc. Natl. Acad. Sci. 93: 6135-39 (1996). At page 6138, the authors have indicated that "gp96 forms a reservoir reflecting the *cellular content of peptides* that acquire access to the ER." (Emphasis added).

[14] This figure is based on an assumption, for the sake of argument only, that there are only 100 different peptides that are non-covalently bound to hsp in a purified population of gp-96 complexes. Applicants consider the number 100 to be conservative in light of the comments provided in Nieland (footnote 12). As indicated in footnote 11, a 100 μg sample of gp-96 complexes corresponds to ~ 1 nmole of complexes and, assuming there are 100 different peptides present in this mixture, there would be only 0.01 nmole of any specific gp-96 peptide complex present in the 100 μg sample administered. Since Smilek and Aichele disclose administration of at least 100 nmole of peptide, this represents (100 nmole/0.01 nmole), or 10,000 fold more peptide than administered as described in Examples 1 and 2 on pages 38 to 41 of the specification.

composition comprising a *purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ*, rather than a purified, defined graft-specific antigenic peptide not bound to a heat shock protein.

Accordingly Applicants respectfully submit that one of ordinary skill in the art, at the time this invention was made, would have understood that the claimed invention was not directed toward modulating an immune response directed toward an hsp-bound peptide. Rather, Applicants submit, one of ordinary skill would have understood that a the claimed methods were directed toward suppression of graft rejection by administering a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, which may be autologous or allogeneic, to a patient in need of treatment or prevention of graft rejection.

Therefore one of ordinary skill has been taught that a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, could be isolated from any convenient source (other than cells, tissue, or organ of the graft), according to the methods disclosed in the present specification, whether allogeneic or autologous, and used for the prevention and treatment of graft rejection according the methods disclosed. Therefore one of ordinary skill in the art would appreciate that the nature of the hsp-bound peptide, or even the very presence or absence of a hsp-non-covalently bound peptide, would not be predicted to bear on the successful use of the presently-claimed methods. Consequently, Applicants respectfully submit that the instant specification would have enabled one of ordinary skill in the art at the time the invention was made to practice the full scope of the claimed invention without undue experimentation.

The Examiner also contends that the present specification is not enabling for the claimed invention since "it is not readily apparent from examination of the data presented that the claimed method provides results, in terms of long-term graft survival, which are any

better than controls." [15] The Examiner further contends that the exemplification depicted in Fig. 1 "would not lead the artisan to reasonably predict that the claimed invention would be efficacious in the prevention or treatment of graft rejection." [16] In support of these assertions, the Examiner provides, on pages 3 and 4 of the Office Action, a series of technical comments that are based, in part, upon the Examiner's own professional scientific experience.

Since the Examiner characterizes Applicants' submitted experimental data as no better than the control data and suggests that the present methods would not be efficacious, the Examiner is alleging that the claimed invention is inoperable, and therefore, this aspect of the rejection under 35 U.S.C. § 112, first paragraph, is based upon an alleged lack of utility.

According to the Utility Guidelines, the standard for a utility rejection is the same whether under § 101 or § 112 [17]. "Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper" (M.P.E.P. 2107.IV). An examiner should, in the first instance, defer to the statements regarding utility in the specification as being true, especially when supported by evidence in the record:

> For obvious reasons of efficiency and in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by simply evaluating the logic of the statements made, taking into consideration any evidence cited by the applicant. If the asserted utility is credible (i.e., believable based on the record or the nature of the invention), a rejection based on "lack of utility" is not appropriate. Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons. (M.P.E.P. 2107.01.A.)

In cases in which pharmacological processes are claimed, such as the present application, animal data is particularly relevant in evaluating utility.

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[15] Office Action, pages 3-4.

[16] Office Action, page 3.

[17] Federal Register 66 (4), at 1097 (January 5, 2001); Section II.A.

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process. (M.P.E.P. 2107.02.III.).

Nevertheless, on page 4 of the Office Action, the Examiner contends that following graft survival for ten days is too short a period of time to be predictive of long-term graft survival. In support of this assertion, the Examiner cites his own published work (Vandervegt *et al.*, 1993, J. Exp. Med. 177: 1587-92) (cited by the Examiner as reference "V" on PTO form 892; hereafter "Vandervegt"), in which grafts immunologically predicted to fail had been able to survive for more than ten days. Moreover, the Examiner contends that experimental mice should have carried three separate grafts, *i.e.* two allogeneic and one syngeneic, to provide better control data, since graft failure may be the result of any one of a number of artifactual reasons provided by the Examiner.

In reply, Applicants note that the model system of Vandervegt is very different from that disclosed in the present specification. For example: (1) graft donor and recipient mice in Vandervegt were of the same strain and differed only with respect to gender; (2) the immune system of recipient mice in Vandervegt was generally, rather than specifically and locally, suppressed by administration of anti-CD4+ or anti-CD8+ monoclonal antibodies, prior to grafting; and (3) tail skin grafts were used, rather than the 1.6 cm diameter skin grafts employed in the present experimental protocols. These methodological differences are reflected, for example, in the observation made by the Examiner, that, with respect to the data provided in Fig. 1 of the instant application "[a]ll of the control animals show nearly total graft failure by day 10 post-grafting," [18] in contrast to the system of Vandervegt where grafts immunologically predicted to fail do survive for more than ten days. Accordingly, Applicants submit that since the model system of Vandervegt is so different from that described in the present specification, a direct comparison of graft survival times is not valid.

With respect to the Examiner's specific methodological criticisms and assertions, Applicants note that the experimental procedures used are labor intensive and require careful and precise manipulation of the grafted tissue. The methods employed

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[18] Office Action, page 4.

involve surgical removal of a 1.6 cm diameter portion of skin from a donor mouse and attachment of that portion to a recipient mouse using surgical stitching procedures. Accordingly, Applicants respectfully submit that repeating this procedure three times for each of the 25 mice used, would be, at best, impractical. Applicants submit that three 1.6 cm grafts per mouse would inflict excessive physiological stress on the animal and that multiple, smaller grafts would be difficult to attach surgically with the precision required. Finally, Applicants respectfully submit that, in light of the multitude of factors that would lead to graft failure, all of which would be apparent to those of ordinary skill in the art, any positive results supporting successful skin grafts would be all the more compelling. Although a animal model system has been used that differs from one more familiar to the Examiner, Applicants respectfully submit that such differences are not a sufficient basis for a utility rejection under 35 U.S. C. § 112 (see the discussion of *Nelson*, below).

Applicants further submit that the data summarized in Fig. 1 indicate that there is an improved level of graft survival in those animals administered hsp-peptide complexes, particularly those administered 100 μg of a purified population of hsp-peptide complexes isolated from skin and from liver. In fact the Examiner has also noted that a difference between control and experimental animals exists: "All of the control animals show nearly total graft failure at 10 days post-grafting. The majority of HSP-Ag complex treated animals also show a substantial level of graft failure as well at day 10." [19] Therefore, as noted by the Examiner, by 10 days post-grafting there exists a population, albeit a minority, of treated animals that have not rejected their grafts whereas all of the control animals have. Accordingly, Applicants assert, again, that these data demonstrate an improved level of graft survival in the treated animals. Also, even a temporary prevention of graft rejection is useful and within the scope of the claims. Moreover, the Examiner has come forward with no valid reason to doubt that the grafts would not survive long-term -- *i.e.*, that the claimed invention would not work.

In light of the Examiner's assertions regarding the validity and predictive value of Applicants' data, the Examiner's attention is directed to *Nelson v. Bowler* with respect to threshold requirements for establishing utility using experimental data. In *Nelson*, it was alleged by opponents of the subject patent that utility of the claimed compounds had

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[19] Id.

not been established since data supporting an asserted pharmacological activity had not been obtained using, as an example, a specific experimental protocol generally accepted as providing statistically significant data. In reply, the court stated that "rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response." [20] That is, as long as there is a reasonable correlation between the data generated using an animal model and the claimed therapeutic application, such data will "almost invariably be sufficient to establish therapeutic or pharmacological utility for a ... process." (M.P.E.P. 2107.02.III)

The basis for accepting such data as adequate proof of utility was provided by the court *In re Brana*, quoting *In re Kimmel*:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans. [21]

Applicants' data, as presented in Fig. 1, demonstrate improved survival of skin grafts in those animals administered a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide as compared to control animals. Applicants therefore submit that there is a reasonable correlation between the claimed methods for prevention and treatment of graft rejection and the data provided. Accordingly, Applicants respectfully submit that the data provided is, at a minimum, sufficient to meet the legally-established threshold for utility.

In summary, the present specification teaches a method for the treatment and prevention of graft rejection comprising administering a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide. The specification has also taught that the claimed methods are mediated by the properties of the administered heat shock proteins, *per se*, and are not dependent upon modulation of an immune response directed toward a graft-specific antigen. Accordingly, the

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[20] *Nelson v. Bowler* 626 F.2d 853, 856 (Fed. Cir. 1980)

[21] *In re Brana* 51 F.3d 1560, 1567 (Fed. Cir. 1995).

presently-claimed methods are both flexible and powerful because they do not require the identification and isolation of any particular graft-specific antigen against which a graft rejection response may be elicited. This aspect of the present invention is particularly important in those instances in which graft rejection is directed against more than one antigen. [22]

Consequently, in light of the teaching and the experimental data provided by the instant specification (summarized above), Applicants submit that the claimed methods have utility and are fully enabled, and, further, that one of ordinary skill in the art would reasonably predict, at a minimum, that the presently claimed methods would more likely than not be efficacious for the prevention and treatment of graft rejection. Accordingly, Applicants respectfully request that the rejection of claims 1-2 and 6-21 for lack of enablement under 35 U.S.C. § 112, first paragraph, be withdrawn. Since claim 3 has been canceled, Applicants respectfully submit that the rejection of claim 3 under 35 U.S.C. § 112, first paragraph, is now moot. Accordingly, Applicants respectfully request that the rejection of claim 3 for lack of enablement under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Rejection Under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn

Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. On page 4 of the Office Action, it has been asserted that the phrase "the antigenic molecule is not an alloantigen of the grafted cells" is ambiguous and unclear.

In reply, Applicants first note that the although claim 3 has been canceled, the subject phrase has been amended to recite "the peptide is not an alloantigen of the grafted cells, tissue, or organ" and has been incorporated into claim 1. Applicants direct the Examiner's attention to the section of the specification as filed spanning page 9, line 36, to page 10, line 4, which discloses that:

> in a specific embodiment for hsp-peptide complexes used in accordance with the invention, the complexed peptide is not an alloantigen of the grafted tissue

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[22] See for example, Tisch at page 437: "Inducing clonal deletion/anergy with whole antigen or peptide may prove to be effective in instances in which the inciting autoantigen has been identified .... However, the high degree of specificity required for the process of clonal deletion/anergy may be limiting when...there are responses to several autoantigens (as many as six to eight in IDDM) and the critical inciting autoantigen(s) is not known."

against which a graft rejection response may be elicited. For example, and not by way of limitation, an autologous hsp-peptide complex would be substantially free of any alloantigen.

Therefore, the phrase "an alloantigen of the grafted cells" clearly refers to a peptide of the same allotype as the donor. Accordingly, the phrase "the peptide is not an alloantigen of the grafted cells" refers to a peptide that is foreign to the donor in that it is not the same allotype as the donor, and may or may not be foreign to the recipient. Consequently, Applicants respectfully submit that claim 3 was not ambiguous or unclear.

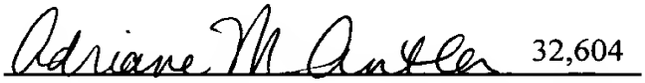
Since claim 3 has been canceled, Applicants respectfully submit that the rejection of claim 3 under 35 U.S.C. § 112, second paragraph, is now moot. Accordingly, Applicants respectfully request that the rejection of claim 3 under 35 U.S.C. § 112, second paragraph, be withdrawn.

CONCLUSION

Applicants believe that each ground for rejection of the pending claims has been successfully overcome or obviated. Accordingly, Applicants respectfully request that the rejection of claims 1-3, and 6-20 under 35 U.S.C. § 112, first paragraph, and the rejection of claim 3 under 35 U.S.C. § 112, second paragraph, be withdrawn. Applicants submit that the entire application in now in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

Date: December 18, 2001



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Enclosure

Application of: SRIVASTAVA

Application No.: 09/393,652 Group Art Unit: 1644

Filed: September 10, 1999 Examiner: F. Pierre VanderVegt, Ph.D.

For: METHODS AND COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF GRAFT REJECTION USING HEAT SHOCK PROTEINS

Attorney Docket No.: 8449-025-999

Appendix A: Marked-up Version of the Amended Paragraph

On page 7, please amend the paragraph beginning "Methods and compositions for the treatment and prevention of graft rejection," as follows, where matter to be deleted is enclosed in brackets and matter that has been added is indicated by underlining:

Methods and compositions for the treatment and prevention of graft rejection are described. The invention is based, in part, on newly discovered immunotherapeutic and immunoprophylactic treatment regimens for graft rejection. In contrast to other methods reported in the literature, the use of hsps in accordance with the present invention [are] is not dependent of administration of any particular target antigen of the rejection process.

Application of: SRIVASTAVA

Application No.: 09/393,652 Group Art Unit: 1644

Filed: September 10, 1999 Examiner: F. Pierre VanderVegt, Ph.D.

For: METHODS AND COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF GRAFT REJECTION USING HEAT SHOCK PROTEINS

Attorney Docket No.: 8449-025-999

Appendix B: Marked-up Version of the Claims Amended Herein

Matter that has been deleted is enclosed in brackets, while that added is underlined.

1. (Amended) A method of preventing or treating rejection of a grafted cell, tissue, or organ in a mammal comprising administering to the mammal a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to [an antigenic molecule] a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ.

6. (Amended) The method of Claim 1 [or 4], wherein the grafted cell, tissue, or organ is skin, liver, kidney, heart, bone marrow, pancreas, lung, cornea, cartilage, or a cell derived therefrom.

8. (Amended) The method of Claim 1 [or 4], wherein the heat shock protein is mammalian.

13. (Amended) The method of Claim 1[,] or 2,[3, 4, or 5,] wherein the mammal is human.

14. (Amended) The method of Claim 1 [or 4], comprising administering the [heat shock protein] composition before the cell, tissue, or organ is grafted.

15. (Amended) The method of Claim 1 [or 4], comprising administering the [heat shock protein] composition after the cell, tissue, or organ is grafted.

16. (Amended) The method of Claim 1 [or 4], wherein the amount of the heat shock protein present in the composition is in a range of 5 μg to 5,000 μg.

17. (Amended) The method of Claim 1 [or 4], wherein the amount of the heat shock protein present in the composition is 100 μg or more.

18. (Amended) The method of Claim 1 [or 4], wherein the amount of the heat shock protein present in the composition is 200 μg or more.

20. (Amended) The method of Claim 1 [or 4], wherein the heat shock protein is not hsp60.

21. (Amended) The method of Claim 1, wherein the [antigenic molecule] peptide is not a bacterial peptide.

32. (New) The method of claim 1, wherein said composition comprises a purified population of complexes, each complex in said population consisting essentially of a heat shock protein non-covalently bound to a peptide, and wherein each peptide is independently selected from a population of different peptides.

Application of: SRIVASTAVA

Application No.: 09/393,652 Group Art Unit: 1644

Filed: September 10, 1999 Examiner: F. Pierre VanderVegt, Ph.D.

For: METHODS AND COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF GRAFT REJECTION USING HEAT SHOCK PROTEINS

Attorney Docket No.: 8449-025-999

Appendix C: The Claims As They Will Be Pending Upon Entry of the Present Amendment Dated December 18, 2001

1. (Amended) A method of preventing or treating rejection of a grafted cell, tissue, or organ in a mammal comprising administering to the mammal a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ.

2. The method of Claim 1, wherein the heat shock protein is not an alloantigen of the grafted cells, tissue, or organ.

6. (Amended) The method of Claim 1, wherein the grafted cell, tissue, or organ is skin, liver, kidney, heart, bone marrow, pancreas, lung, cornea, cartilage, or a cell derived therefrom.

7. The method of Claim 6, wherein the grafted cell or tissue is skin or a cell derived from skin.

8. (Amended) The method of Claim 1, wherein the heat shock protein is mammalian.

9. The method of Claim 8, wherein the heat shock protein is human.

10. The method of Claim 8, wherein the heat shock protein is gp96.

11. The method of Claim 8, wherein the heat shock protein is hsp70.

12. The method of Claim 8, wherein the heat shock protein is hsp90.

13. (Amended) The method of Claim 1 or 2, wherein the mammal is human.

14. (Amended) The method of Claim 1, comprising administering the composition before the cell, tissue, or organ is grafted.

15. (Amended) The method of Claim 1, comprising administering the composition after the cell, tissue, or organ is grafted.

16. (Amended) The method of Claim 1 wherein the amount of the heat shock protein present in the composition is in a range of 5 μg to 5,000 μg.

17. (Amended) The method of Claim 1, wherein the amount of the heat shock protein present in the composition is 100 μg or more.

18. (Amended) The method of Claim 1, wherein the amount of the heat shock protein present in the composition is 200 μg or more.

19. The method of Claim 14, further comprising administering to the mammal a sample of cells or tissue obtained from the cell, tissue, or organ donor prior to administration of the heat shock protein.

20. (Amended) The method of Claim 1, wherein the heat shock protein is not hsp60.

21. (Amended) The method of Claim 1, wherein the peptide is not a bacterial peptide.

32. (New) The method of claim 1, wherein said composition comprises a purified population of complexes, each complex in said population consisting essentially of a heat shock protein non-covalently bound to a peptide, and wherein each peptide is independently selected from a population of different peptides.